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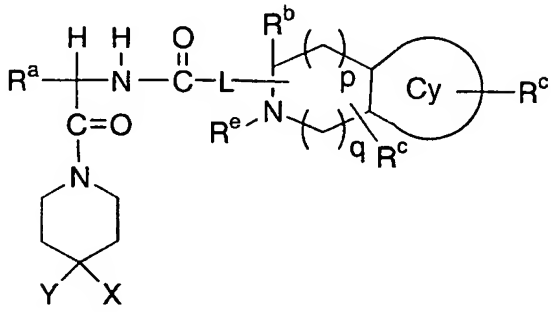
(54) Title: SUBSTITUTED PIPERIDINES AS MELANOCORTIN-4 RECEPTOR AGONISTS

(57) Abstract: Certain novel substituted piperidine compounds are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction. Also provided are methods of treating sexual dysfunction with a compound that is a selective agonist of MC-4R over any other human melanocortin receptor.

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt thereof; wherein

Cy is (1) aryl,
(2) 5- or 6-membered heteroaryl,
(3) 5- or 6-membered heterocyclyl, or
(4) 5-to 7-membered carbocyclyl;

L is $(CR^bR^b)_m$;

m is 0, 1 or 2;

n is 0, 1, 2, or 3;

p is 0, 1 or 2;

q is 0, 1 or 2;

R^a is (1) hydrogen,
(2) C_{1-8} alkyl,
(3) $(CHR^b)_n$-C_{3-7}cycloalkyl,
(4) $(CHR^b)_n$aryl,
(5) $(CHR^b)_n$heteroaryl, or
(6) $(CHR^b)_n$-O(CHR^b)aryl;

in which alkyl is optionally substituted with from 1 to 3 groups independently selected from Rg; aryl, heteroaryl and cycloalkyl are optionally substituted with 1 to 3 groups independently selected from R^f;

R^b is (1) hydrogen,
(2) C_{1-8}alkyl,
(3) $(CH_2)_nC_{3-7}$cycloalkyl, or
(4) $(CH_2)_n$-aryl;

R^c is (1) hydrogen or
(2) a group selected from R^f;

R^d is (1) hydrogen,
(2) C_{1-8}alkyl,
(3) $(CH_2)_n$-aryl,
(4) $(CH_2)_nC_{3-7}$cycloalkyl or
(5) $(CH_2)_n$-heteroaryl;
wherein alkyl and cycloalkyl are optionally substituted with 1 to 3 groups selected from Rg; and cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 3 groups selected from R^f; or
two R^d groups together with the atoms to which they are attached form a 5- or 6- membered ring optionally containing an additional heteroatom selected from O, S, and NR^b;

R^e is (1) a group selected from R^d,
(2) COR^d,
(3) SO_2R^d, or
(4) $COC(R^b)(R^b)N(R^d)(R^d)$;

R^f is (1) a group selected from Rg, or
(2) C_{1-8} alkyl;

Rg is (1) $(CH_2)_n$-aryl,
(2) $(CH_2)_nC_{3-7}$cycloalkyl,
(3) $(CH_2)_n$-heteroaryl,
(4) halo,
(5) OR^b,
(6) $NHSO_2R^b$,
(7) $N(R^b)_2$,

(8) C≡N,
(9) CO_2R^b,
(10) $C(R^b)(R^b)N(R^b)_2$,
(11) NO_2,
(12) $SO_2N(R^b)_2$,
(13) $S(O)_mR^b$,
(14) CF_3, or
(15) OCF_3;

X is
(1) hydrogen,
(2) C_{1-8} alkyl,
(3) $(CH_2)_nC_{3-8}$cycloalkyl,
(4) $(CH_2)_n$aryl,
(5) $(CH_2)_n$heteroaryl,
(6) $(CH_2)_n$heterocyclyl,
(7) C≡N,
(8) $(CH_2)_nCON(R^dR^d)$,
(9) $(CH_2)_nC(O)OR^d$,
(10) $(CH_2)_nNR^dC(O)R^d$,
(11) $(CH_2)_nNR^dC(O)OR^d$,
(12) $(CH_2)_nNR^dC(O)N(R^d)_2$,
(13) $(CH_2)_nNR^dSO_2R^d$,
(14) $(CH_2)_nS(O)mR^d$,
(15) $(CH_2)_nSO_2N(R^d)(R^d)$,
(16) $(CH_2)_nOR^d$,
(17) $(CH_2)_nOC(O)R^d$,
(18) $(CH_2)_nOC(O)OR^d$,
(19) $(CH_2)_nOC(O)N(R^d)_2$,
(20) $(CH_2)_nN(R^d)(R^d)$,
(21) $(CH_2)_nNR^dSO_2N(R^d)(R^d)$;

wherein the cycloalkyl, aryl and heteroaryl groups are optionally substituted with 1 to 3 groups selected from R^f; the heterocyclyl group is optionally substituted with 1 to 3 groups selected from R^f and oxo;

and the $(CH_2)_n$ and alkyl groups are optionally substituted with 1 to 3 groups selected from Rg; and

Y is (1) hydrogen,
(2) C_{1-8}alkyl,
(3) $(CH_2)_nC_{3-8}$cycloalkyl,
(4) $(CH_2)_n$aryl,
(5) $(CH_2)_n$heterocyclyl, or
(6) $(CH_2)_n$heteroaryl;

wherein the cycloalkyl, aryl and heteroaryl groups are optionally substituted with 1 to 3 groups selected from R^f; heterocyclyl group is optionally substituted with 1 to 3 groups selected from R^f and oxo; and the alkyl group is optionally substituted with 1 to 3 groups selected from Rg;

with the proviso that X and Y are not both hydrogen.

2. The compound of Claim 1 wherein Cy is selected from the group consisting of benzene, pyridine, pyrazine, piperidine, imidazole and cyclohexane.

3. The compound of Claim 2 wherein Cy is benzene, pyrazine, or cyclohexane.

4. The compound of Claim 1 wherein L is $(CH_2)_m$ wherein m is 0, 1 or 2.

5. The compound of Claim 1 wherein R^a is $CH(R^b)$-aryl, $CH(R^b)$-OCH_2aryl, or $CH(R^b)$-heteroaryl wherein aryl or heteroaryl is optionally substituted with one or two Rg groups.

6. The compound of Claim 5 wherein R^a is benzyl optionally substituted with one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, and OCF_3.

7. The compound of Claim 6 wherein R^a is 4-chlorobenzyl or 4-fluorobenzyl.

8. The compound of Claim 1 wherein R^b attached to the bicyclic ring of formula I is H or CH_3.

9. The compound of Claim 1 wherein X is C_{1-8}alkyl, $(CH_2)_n$-C_{3-7}cycloalkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_nC(O)N(R^d)(R^d)$, $(CH_2)_nC(O)OR^d$, $(CH_2)_nOR^d$, $(CH_2)_nNHC(O)Rd$, $(CH_2)_nN(R^d)SO_2R^d$, or $(CH_2)_nSR^d$, wherein the cycloalkyl, aryl and heteroaryl groups are optionally substituted with 1 to 3 groups selected from R^f; heterocyclyl is optionally substituted with 1 to 3 groups selected from R^f and oxo; and the $(CH_2)_n$ and alkyl groups are optionally substituted with 1 to 3 groups selected from R^b, halo, $S(O)mR^b$, $N(Rb)_2$, and OR^b.

10. The compound of Claim 9 wherein X is CH_2-heteroaryl, CH_2-heterocyclyl, $NHC(O)R^d$, $C(O)OR^d$, $CH_2N(R^d)SO_2R^d$ or $C(O)N(R^d)(R^d)$, wherein heteroaryl is optionally substituted with 1 to 3 group selected from R^f; heterocyclyl is optionally substituted with 1 to 3 groups selected from R^f and oxo; and wherein R^d is each independently selected from H and C_{1-6} alkyl optionally substituted with OR^b, SR^b, or $N(R^b)_2$, or 2 R^d groups together with the nitrogen to which they are attached form a 5- or 6-membered ring optionally having an additional heteroatom selected from O, S and NR^b.

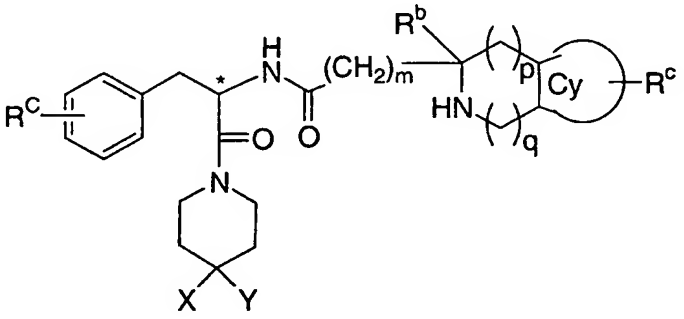
11. The compound of Claim 10 wherein heteroaryl is selected from pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl.

12. The compound of Claim 1 wherein Y is $(CH_2)_nC_{3-7}$ cycloalkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl or $(CH_2)_n$-heteroaryl wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 3 groups selected from R^f, and heterocyclyl is optionally substituted with 1 to 3 groups selected from R^f and oxo.

13. The compound of Claim 12 wherein Y is cyclohexyl, cycloheptyl, cyclopentyl, cyclobutylmethyl, hexyl, tetrahydropyranyl, phenyl, naphthyl, pyridyl, thienyl or furanyl.

14. The compound of Claim 13 wherein Y is cyclohexyl, tetrahydropyranyl, or phenyl.

15. The compound of Claim 1 of formula Ia:



Ia

or a pharmaceutically acceptable salt thereof; wherein

Cy is (1) phenyl,
(2) pyridyl,
(3) piperidinyl,
(4) imidazolyl,
(5) cyclohexyl, or
(6) pyrazinyl;

m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

q is 1 or 2;

R^b is (1) hydrogen,
(2) C_{1-8}alkyl, or
(3) C_{3-6}cycloalkyl;

R^c is (1) hydrogen,

(2) halo,
(3) C_{1-8}alkyl, or
(4) C_{3-6}cycloalkyl,
(5) OR^b,
(6) CF_3,
(7) OCF_3,
(6) $S(O)_mR^b$, or
(7) $N(R^b)(R^b)$;

R^d is (1) hydrogen,
(2) C_{1-5}alkyl, optionally substituted with OR^b, NR^bR^b, or SR^b,
(3) aryl,
(4) heteroaryl,
(5) C_{5-6}cycloalkyl, or
two R^d together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing an additional heteroatom selected from O, S and NR^b;

X is (1) hydrogen,
(2) $C(O)OR^d$,
(3) $C(O)N(R^d)(R^d)$,
(4) $NHC(O)R^d$,
(5) $NHC(O)NHR^d$,
(6) $NHC(O)OR^d$,
(7) $NHSO_2R^d$,
(8) $OC(O)R^d$,
(9) C_{1-6}alkyl,
(10) CH_2-C_{3-7}cycloalkyl,
(11) $(CH_2)_n$-aryl, optionally substituted with 1 to 3 groups selected from halogen, $C(O)OR^b$, and tetrazole,
(12) $(CH_2)_n$-heteroaryl, optionally substituted with C_{1-3}alkyl, $N(R^b)(R^b)$ or OR^b,
(13) $(CH_2)_n$-heterocyclyl optionally substituted with 1 to 3 groups selected from C_{1-3} alkyl and oxo,
(14) CH_2-OR^d,

(15) $(CH_2)_nS(O)_mR^d$,
(16) $(CH_2)_nN(Rd)SO_2R^d$,
(17) $(CH_2)_nC(O)R^d$, or
(18) S-heteroaryl;

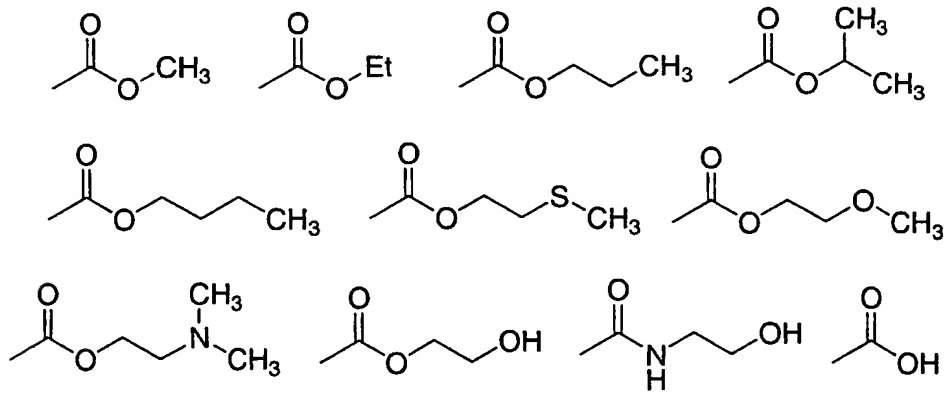
Y is (1) hydrogen,
(2) C_{1-8}alkyl,
(3) C_{3-7}cycloalkyl,
(4) $(CH_2)_n$aryl,
(5) $(CH_2)_n$heteroaryl, or
(6) $(CH_2)_n$heterocyclyl;

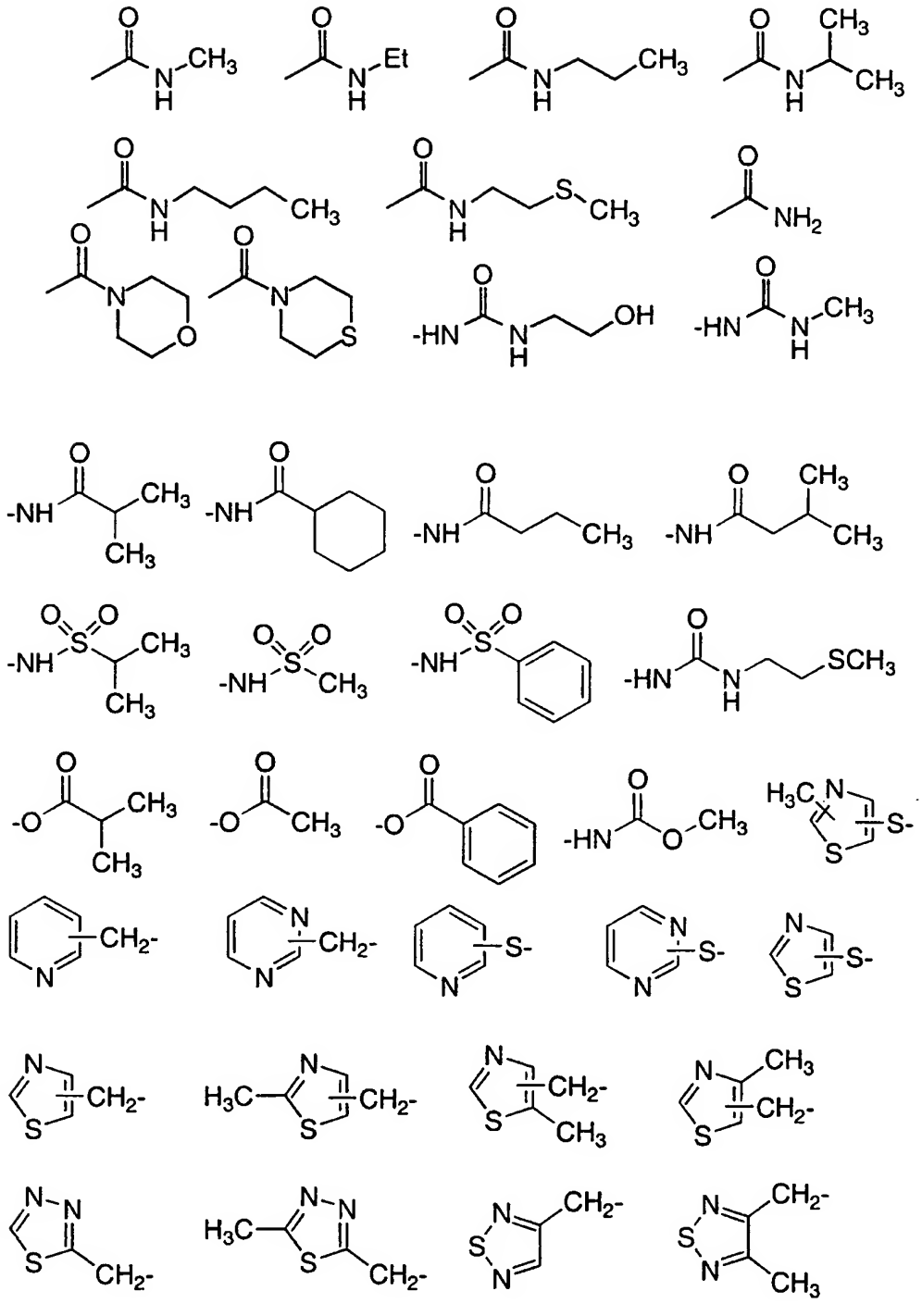
wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with one or two halo groups;

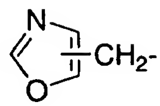
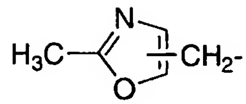
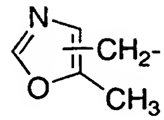
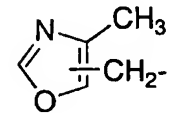
with the proviso that X and Y are not both hydrogen.

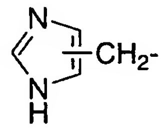
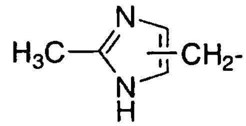
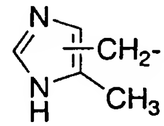
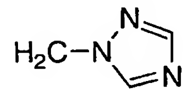
16. The compound of Claim 15 wherein the carbon atom marked with * has the *R* configuration.

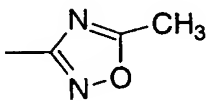
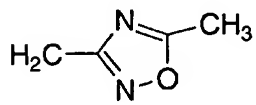
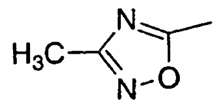
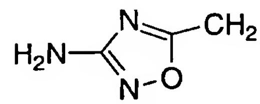
17. The compound of Claim 15 wherein X is selected from the group consisting of:

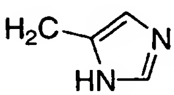
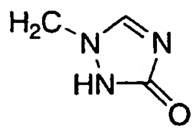
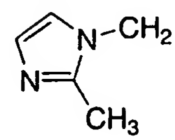
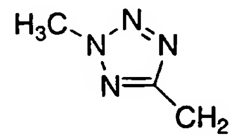


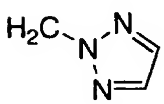
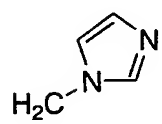
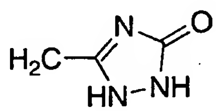
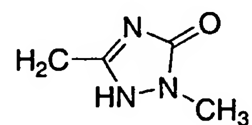


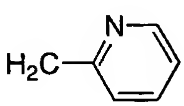
   

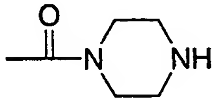
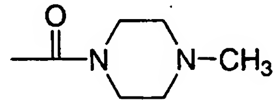
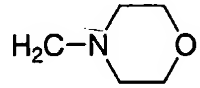
   

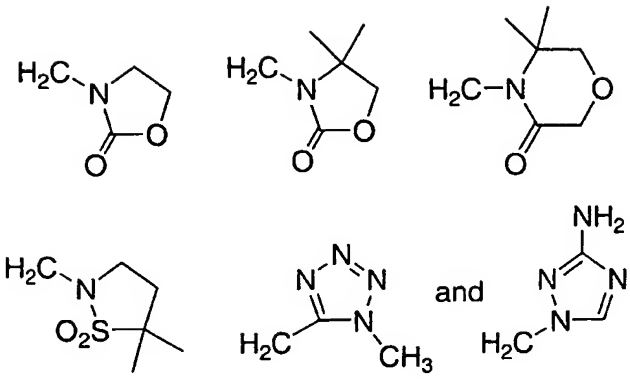


-NH-C(O)CH_3 -C(O)N$(CH_3)_2$ -C(O)NH-t-Bu

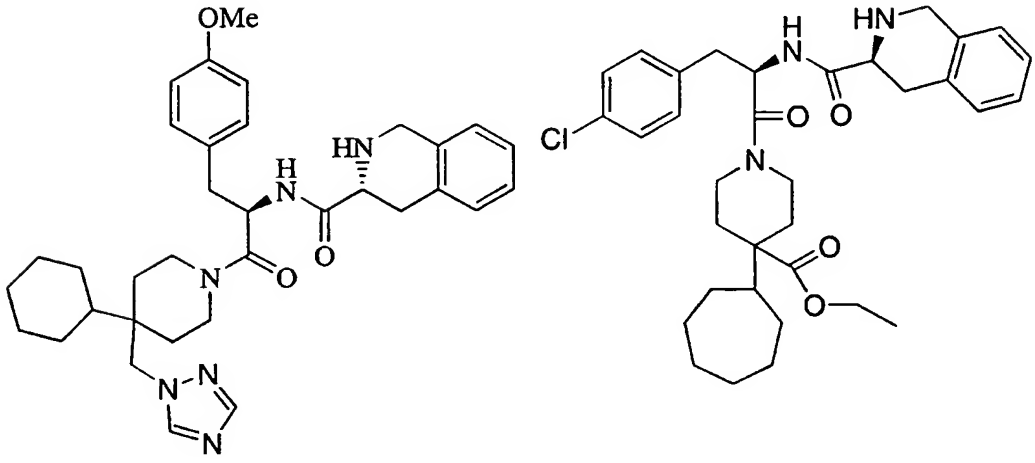
-CH_2S(O)CH$(CH_3)_2$ -C(O)NHCH_2CH_2N$(CH_3)_2$ C(O)CH$(CH_3)_2$

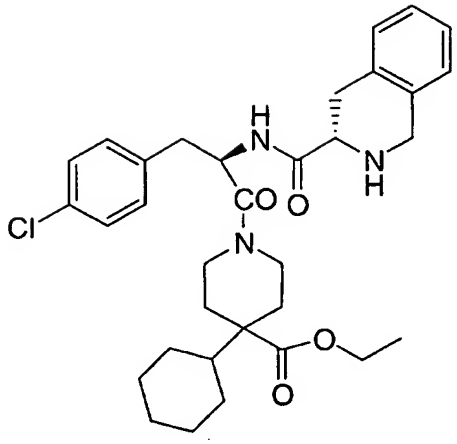
-CH_2S$(O)_2$CH$(CH_3)_2$ -CH_2N(iPr)SO_2CH_3

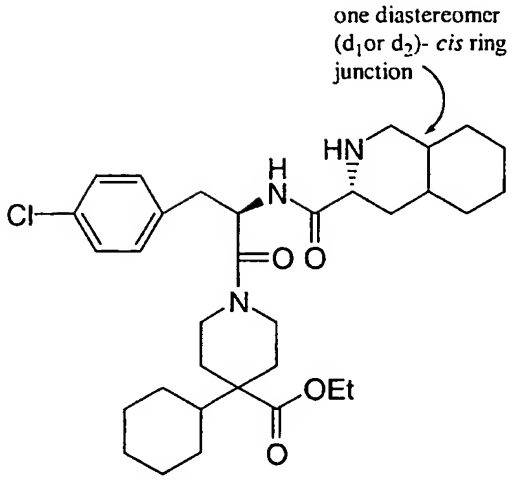
  

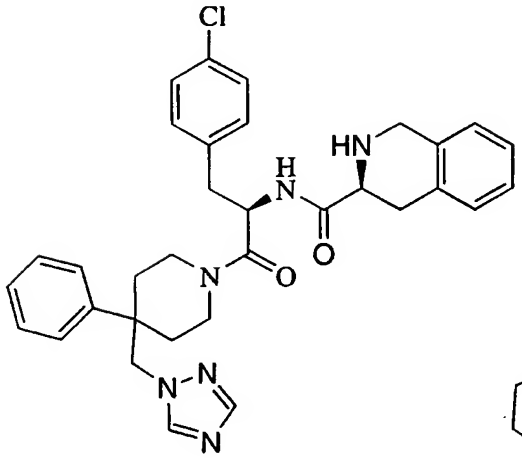


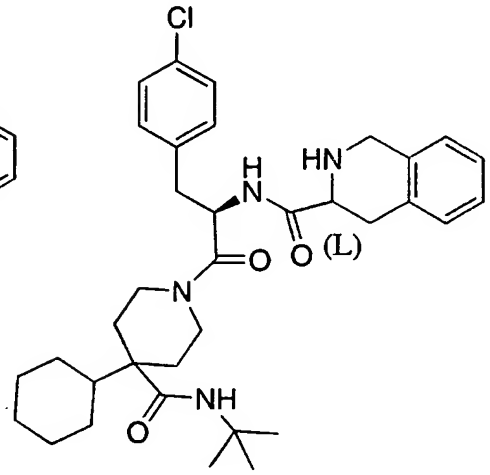
18. The compound of Claim 15 selected from the group consisting of:











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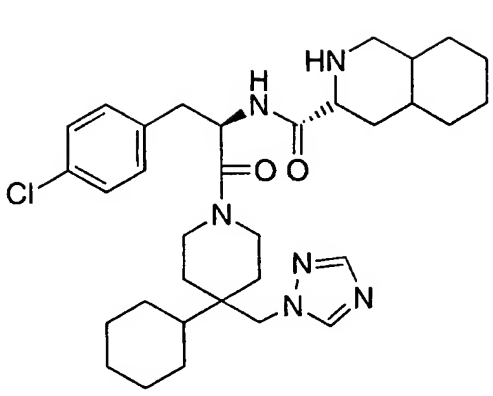

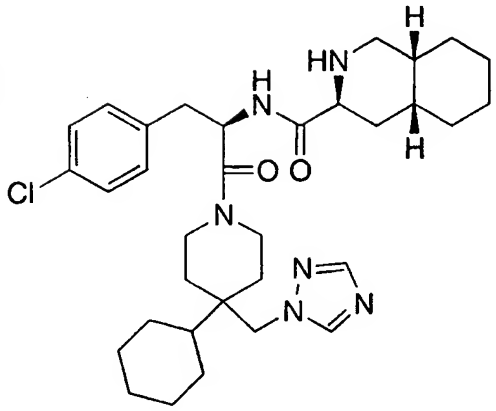

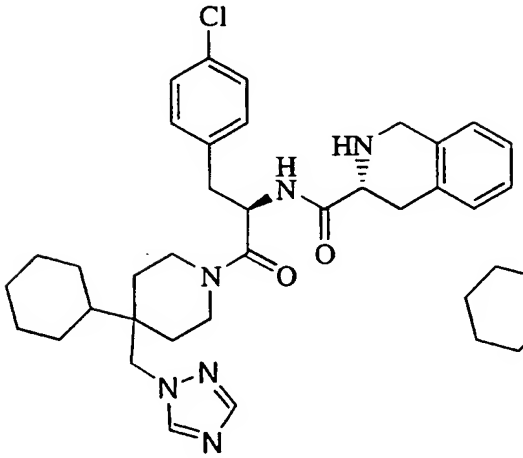

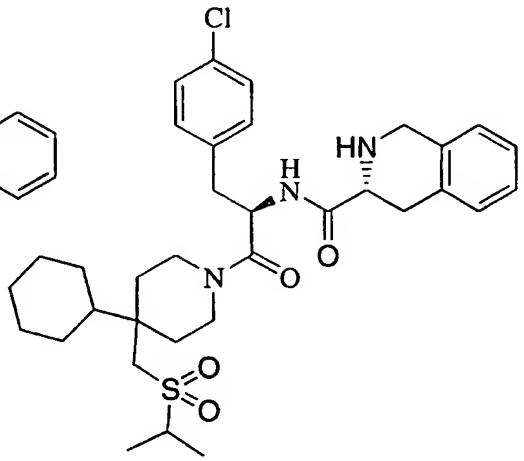

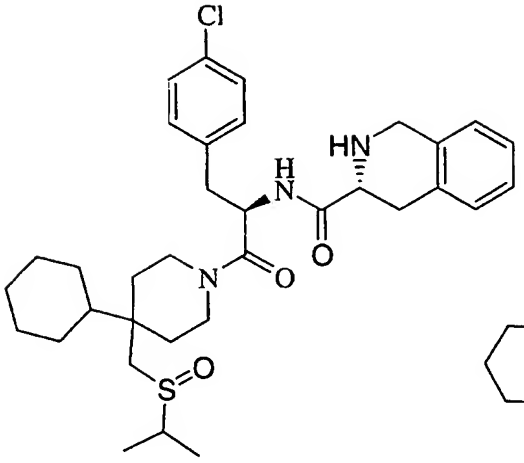

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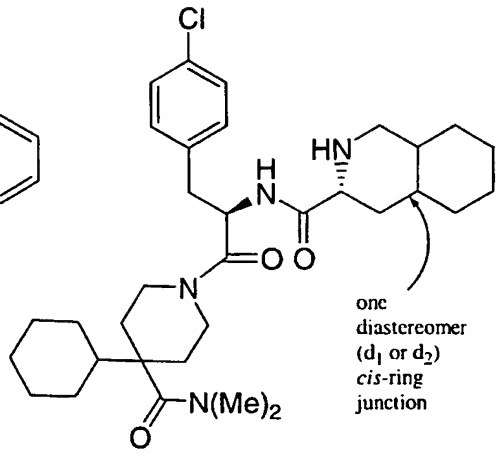

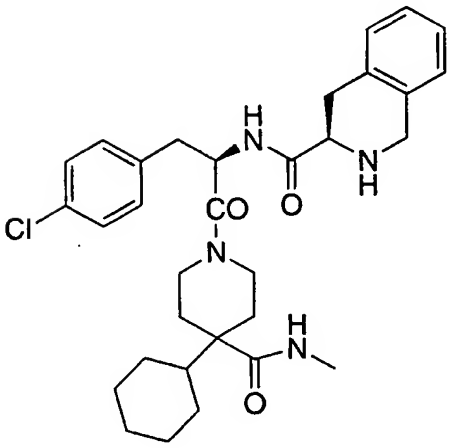

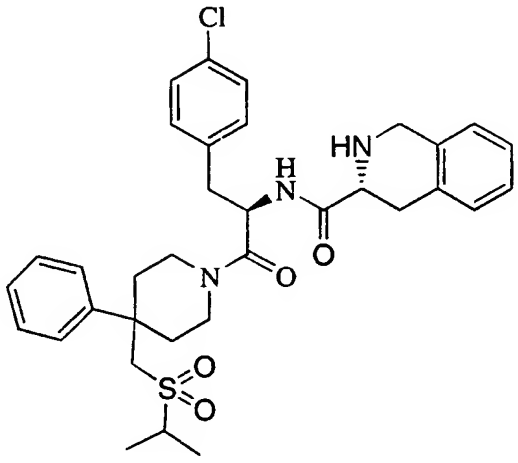

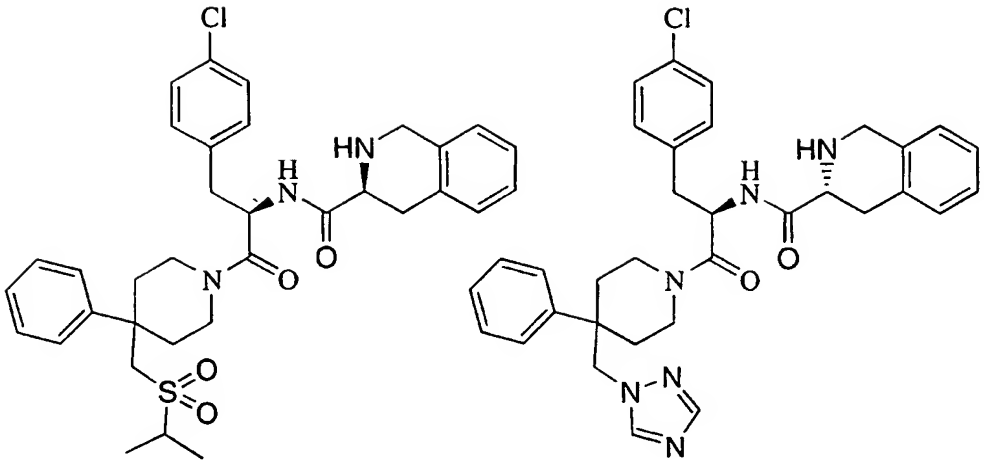

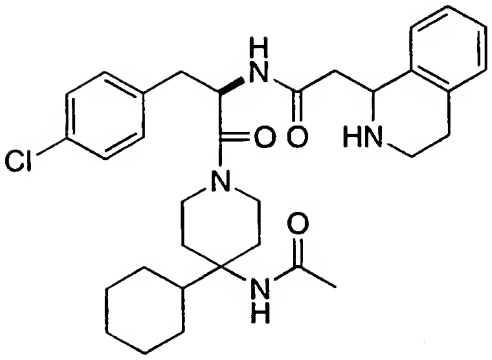

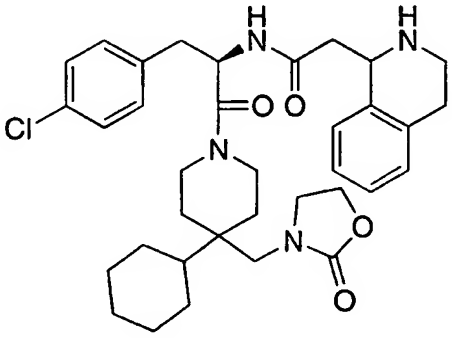

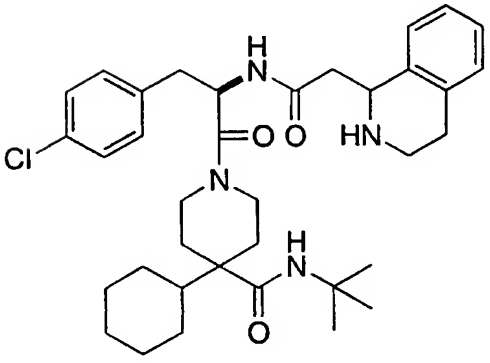

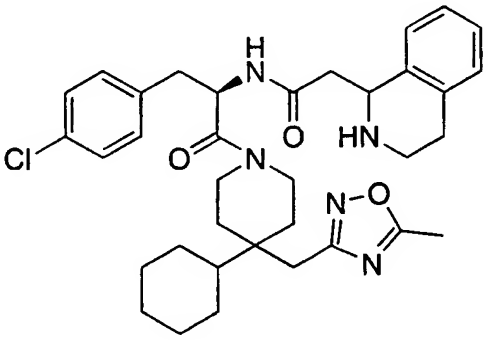

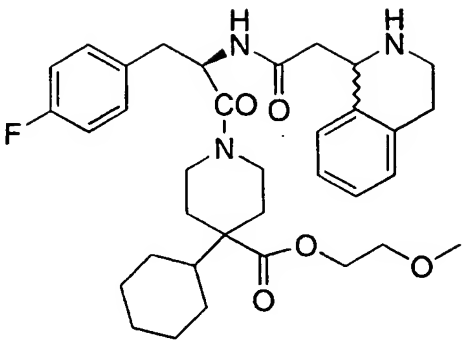

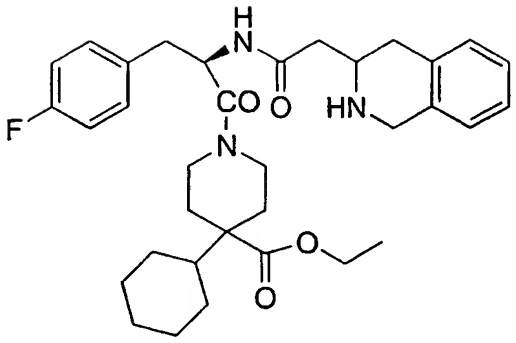

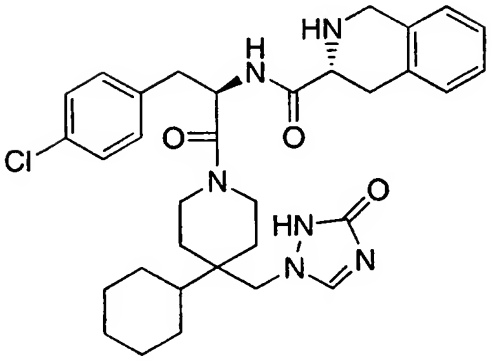

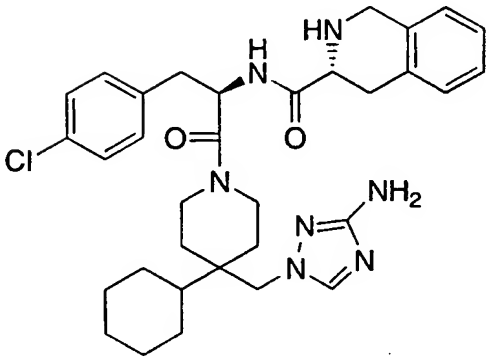

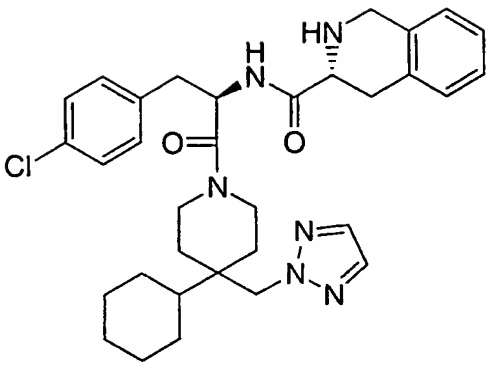

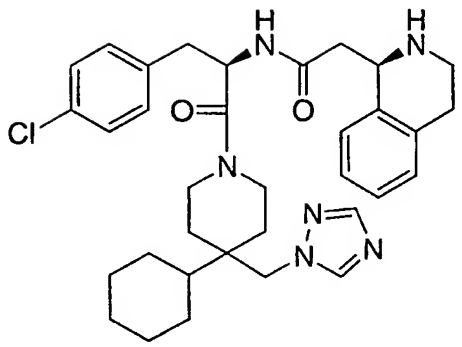

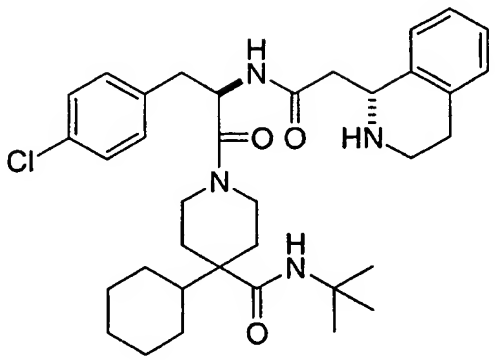

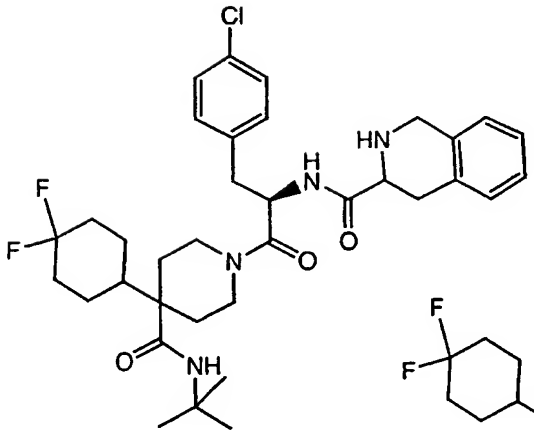

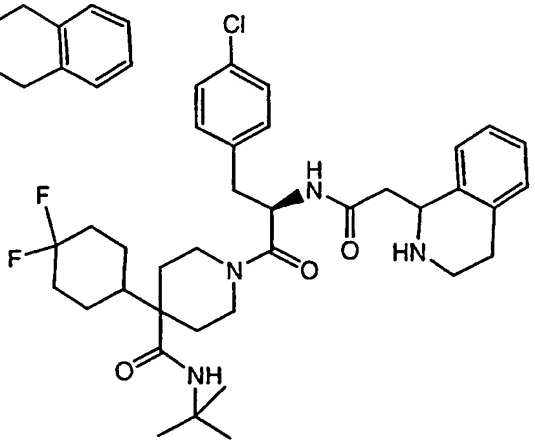

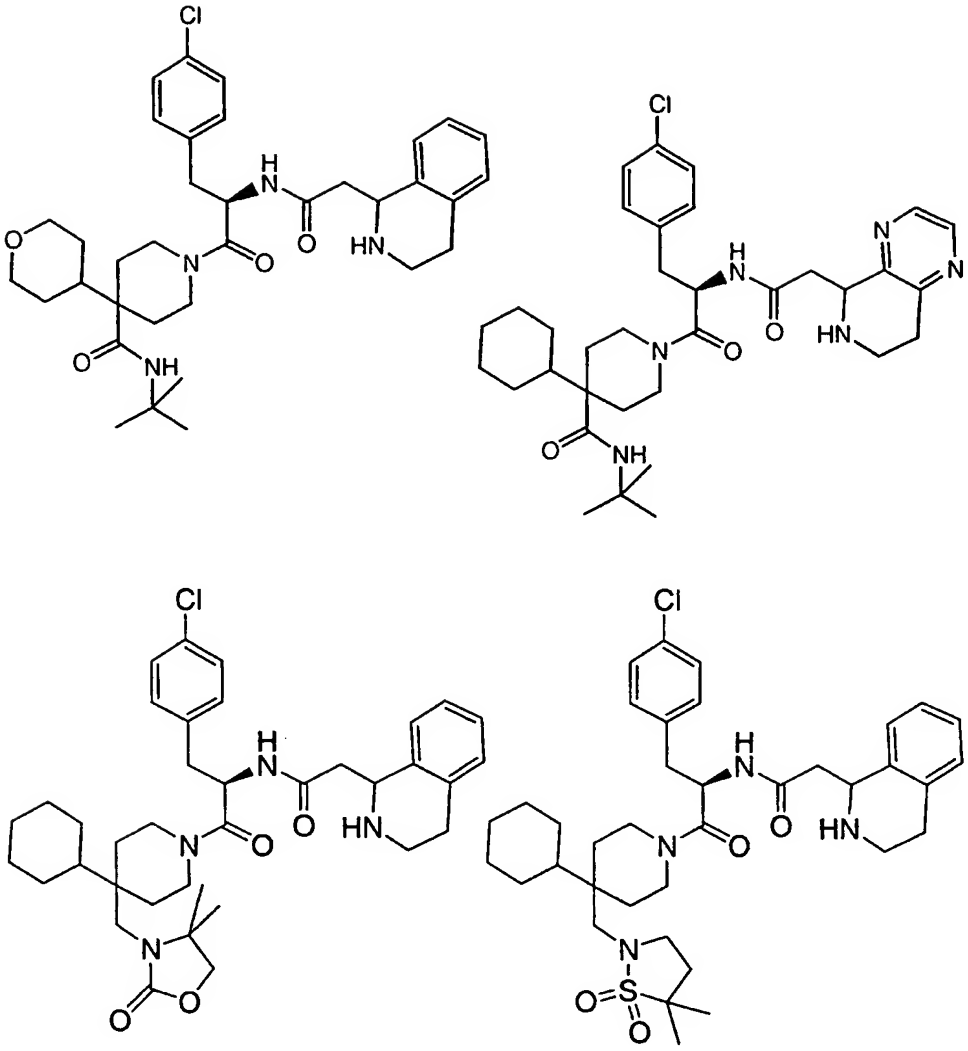

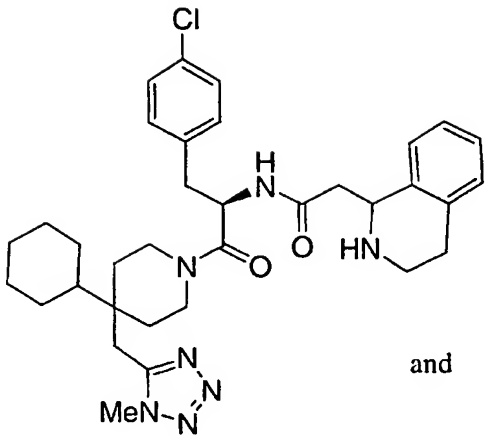

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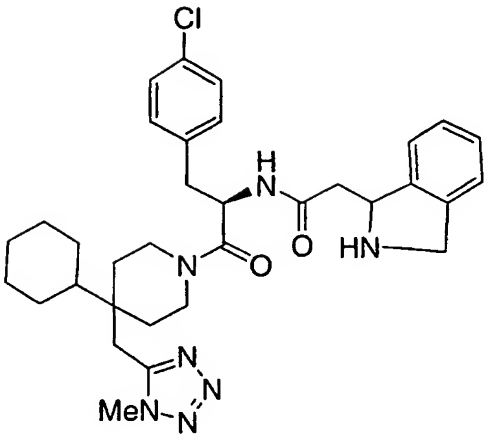

19. A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of the human melanocortin-4 receptor which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

20. A method for the treatment or prevention of obesity which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

21. A method for the treatment or prevention of diabetes mellitus which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

22. A method for the treatment or prevention of male or female sexual dysfunction which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

23. A method for the treatment or prevention of erectile dysfunction which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

24. A method for the treatment or prevention of female sexual dysfunction which comprises administering to a subject in need of such treatment or prevention an effective amount of a compound of Claim 1.

25. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

26. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human melanocortin-4 receptor (MC-4R) agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nanomolar (nM) and the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 30 nM.

27. The method of Claim 26 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 100 nM.

28. The method of Claim 26 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 1000 nM.

29. The method of Claim 26 wherein the binding of the compound to the human MC-1R is characterized by an IC_{50} greater than 2100 nM.

30. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 30 nM.

31. The method of Claim 30 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 100 nM.

32. The method of Claim 30 wherein the binding of the compound to the human MC-3R is characterized by an IC_{50} greater than 540 nM.

33. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the binding of the compound to the human MC-4R is characterized by an IC_{50} less than 30 nM and the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 30 nM.

34. The method of Claim 33 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} of greater than 100 nM.

35. The method of Claim 33 wherein the binding of the compound to the human MC-5R is characterized by an IC_{50} greater than 230 nM.

36. The method of Claim 26 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 30 nM.

37. The method of Claim 27 wherein the compound is further characterized by binding to each of the human MC-2R, MC-3R, and MC-5R with an IC_{50} greater than 100 nM.

38. The method of Claim 28 wherein the compound is further characterized by binding to each of the human MC-2R and MC-3R with an IC_{50} greater than 540 nM and binding to the MC-5R with an IC_{50} greater than 230 nM.

39. The method of Claim 36 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 30 nM.

40. The method of Claim 37 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 100 nM.

41. The method of Claim 38 wherein the compound is further characterized by binding to any other human melanocortin receptor with an IC_{50} greater than 500 nM.

42. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

43. The method of Claim 42 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

44. The method of Claim 42 wherein the compound binds to the human MC-4R with a binding affinity at least 1000-fold higher than the compound binds to each of the human MC-1R and MC-2R, at least 580-fold higher than the compound binds to the human MC-3R, and at least 250-fold higher than the compound binds to the human MC-5R.

45. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the compound binds to the human MC-4R with a binding affinity at least 10-fold higher than the compound binds to any other human melanocortin receptor.

46. The method of Claim 45 wherein the compound binds to the human MC-4R with a binding affinity at least 100-fold higher than the compound binds to any other human melanocortin receptor.

47. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the

functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-1R is characterized by an EC_{50} greater than 10 nM.

48. The method of Claim 47 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 100 nM.

49. The method of Claim 47 wherein the functional activity of the compound at the MC-1R is characterized by an EC_{50} greater than 1200 nM.

50. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-3R is characterized by an EC_{50} greater than 10 nM.

51. The method of Claim 50 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 100 nM.

52. The method of Claim 50 wherein the functional activity of the compound at the MC-3R is characterized by an EC_{50} greater than 1200 nM.

53. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the MC-4R is characterized by an EC_{50} less than 10 nM and the functional activity at the MC-5R is characterized by an EC_{50} greater than 10 nM.

54. The method of Claim 53 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 100 nM.

55. The method of Claim 53 wherein the functional activity of the compound at the MC-5R is characterized by an EC_{50} greater than 520 nM.

56 The method of Claim 47 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 10 nM.

57. The method of Claim 48 wherein the compound is further characterized by having a functional activity at each of the human MC-2R, MC-3R, and MC-5R with an EC_{50} greater than 100 nM.

58. The method of Claim 49 wherein the compound is further characterized by having a functional activity at the human MC-2R and MC-3R with an EC_{50} greater than 1200 nM and a functional activity at the human MC-5R with an EC_{50} greater than 520 nM.

59. A method of treating sexual dysfunction in a male or female subject which comprises administering to the subject in need thereof a therapeutically effective amount of a compound which is a human MC-4R agonist wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 10-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

60. The method of Claim 59 wherein the functional activity at the human MC-4R is characterized by an EC_{50} at least 100-fold lower than the functional activity at each of the human MC-1R, MC-2R, MC-3R, and MC-5R.

61. A method for the oral treatment of sexual dysfunction in a male or female subject which comprises the oral administration to the subject in need thereof a therapeutically effective amount of a compound which is an agonist of the human MC-4R.

62. The method of Claim 61 wherein the compound is a selective agonist of the human MC-4R.

63. The method of Claim 61 wherein the sexual dysfunction is erectile dysfunction.

64. The pharmaceutical composition of Claim 25 further comprising a second active ingredient selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, a sequestrant cholesterol lowering agent, a β3 adrenergic receptor agonist, a neuropeptide Y antagonist, a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, and a dopamine receptor agonist.

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(54) Title: ISOQUINOLINE COMPOUND MELANOCORTIN RECEPTOR LIGANDS AND METHODS OF USING SAME

(57) Abstract

The invention relates to melanocortin receptor ligands and methods of using the ligands to alter or regulate the activity of a melanocortin receptor. The invention further relates to tetrahydroisoquinoline aromatic amines that function as melanocortin receptor ligands and as agents for controlling cytokine-regulated physiologic processes and pathologies, and combinatorial libraries thereof.